UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/812,731 | 03/30/2004 | Choong-Chin Liew | 4231/2055P | 4547 |

29933 7590 10/08/2009

Edwards Angell Palmer & Dodge LLP
111 HUNTINGTON AVENUE
BOSTON, MA 02199

| EXAMINER | |
|---|---|
| SWITZER, JULIET CAROLINE | |
| ART UNIT | PAPER NUMBER |
| 1634 | |
| MAIL DATE | DELIVERY MODE |
| 10/08/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/812,731 | LIEW, CHOONG-CHIN | |
| | Examiner | Art Unit | |
| | Juliet C. Switzer | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *94,96,98,100,104,106,110,112-117 and 120* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *94, 96, 98, 100, 104, 106, 110, 112-117, and 120* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. Claims 94, 96, 98, 100, 104, 106, 110, 112-117, and 120 are pending and under examination.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 112-117 and 120 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims depend from cancelled claims, and thus the claims are indefinite because they are incomplete claims.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 96, 110, 112-117, and 120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. This is a rejection for new matter.

7. Claim 96 recites a method wherein a level of BTG2 gene expression from a test subject is compared with that from subjects who have schizophrenia, and if the expression is lower that the subjects who have schizophrenia, than the test subject is classified as more likely to have schizophrenia than to be healthy. There is no basis in the specification for a method wherein a subject is determined to be more likely to have schizophrenia than to be healthy based on a DIFFERENCE in expression relative to controls that have schizophrenia.

8. Claims 94, 96, 98, 100, 104, 106, 110, 112-117, and 120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

**Nature of the invention**

The invention is drawn to methods for classifying a human test subject as more likely to have schizophrenia, methods for screening a human test subject for being a candidate for having schizophrenia, and methods for detecting expression of a BTG family, member 2 gene in a human test subject. The claims all include a step of quantifying the level RNA encoded by a BTG family, member2 (BTG2) gene in a blood sample obtained from said human and comparing the level with a quantified level of RNA encoded by said gene in blood samples from control subjects having schizophrenia and/or control subjects who are healthy. Claims 100 and 104 all include statements regarding the indication of schizophrenia or lack thereof based upon the comparison of the quantified level and the control levels, and claims 94, 96, 98, 106 and 110

include a step of classifying the test subject as being a candidate for or not being a candidate for having schizophrenia based upon the comparisons.

Claim 96 recites a method wherein a level of BTG2 gene expression from a test subject is compared with that from subjects who have schizophrenia, and if the expression is lower that the subjects who have schizophrenia, than the test subject is classified as more likely to have schizophrenia than to be healthy.

The nature of the invention requires the knowledge of a reliable association between comparing BTG2 expression and the indication that schizophrenia is present or not present in a human.

**Teachings in the Specification/Examples**

Regarding schizophrenia, the specification provides example 27 wherein gene expression profiles of blood samples from individuals having schizophrenia were compared with normal individuals, that is healthy patients. The specification teaches that 1,952 genes were identified as being differentially expressed, and regarding the instant claims, table 3Y provides a list of these genes (Example 27). BTG2 is among the genes.

Table 3Y teaches that the ratio of expression in schizophrenic samples relative to control samples is 2.46, indicating that in the tested samples, BTG2 was expressed, on average at a 2.46 times higher level in schizophrenic patients versus healthy controls. Table 3Y teaches that this result is significant p=0.0076.

There is no data to support claim 96, which finds that when test subject expression is different from that of control subjects classified as having schizophrenia and individual is classified as more likely to have schizophrenia.

The specification further provides example 51 which compares gene expression in patients having schizophrenia versus patients having manic depression syndrome. The specification teaches that 294 genes were identified as being differentially expressed, and regarding the instant claims, table 3AC provides a list of these genes (Example 51). BTG2 is among the genes. The table teaches that there is a p-value of 0.0013 for BTG2 expression, but the specification does not provide any guidance as to the level of "difference" between expression in the two populations, nor does the specification provide any guidance as to the direction of the difference (higher or lower expression) that is expected to be observed for any single pairing of samples.

**State of the Prior Art and Level of Unpredictability**

The expression of genes in example 27 was tested by hybridization of samples to a microarray that contains genetic information for tens of thousands of genes. This technology area is highly unpredictable, and as a result significant guidance is required to practice inventions using this type of data. Lee (Clinical Chemistry, 47:8, 1350-1352 (2001)) teaches that despite the technical accuracy of individual observations on an array, these data "are much more prone to numerous false-positive findings fundamentally because of (a) an extremely large number of observations and (b) a very wide dynamic range of gene expression values obtained from gene chip experiments." In view of these unpredictable aspects of applying such data, Lee teaches that replication is necessary to begin to screen out false positive results. The specification does not teach replication of the disclosed experiments in an external cohort of individuals.

Indeed, the need to replicate findings based on differential expression analysis is supported by other writers in the prior and post-filing date art. Michiels et al. teach that

molecular signatures developed based on differential expression data strongly depend on the selection of patients in the training sets, and advocate the use of validation by repeated random sampling (Michiels et al. Lancet, 2005; 365:488-492). Michiels et al. further teach that studies with larger sample sizes are needed before gene expression profiling can be used in the clinic. In the example relevant to the instant claims, the sample sizes were quite small- namely 4 patients having schizophrenia versus 6 healthy control individuals (Figure 26).

Slonin teaches that a common problem when developing classification schemes based on differential expression data is 'overfitting' the data (Slonin, Nature Genetics Supplement, Vol. 32, December 2002, pages 502-508) . As a consequence, when using differential expression data to develop classification schemes, classification of the training samples may well be perfect but subsequent attempts to classify new test data fail miserably. Here there has been no attempt to validate the classification scheme based on BTG2, and so it remains highly unpredictable as to whether or not classification based on relative expression of this gene would be successful. Baker also cautions that in the development of classifiers a major problem is 'overfitting' meaning that if one investigates enough classification rules, then by chance one of them is likely to perform well, and that data from samples used to develop classifiers should be split to create samples for validations (p.512, right col., lns.1-8), and that larger sample sizes should be used (p.513, left col., lns.17-31) (Baker. Journal of the National Cancer Institute, Vol. 95, No. 7, April 2, 2003).

Iwamoto et al. teach that expression profiling in psychiatric fields have been notoriously discordant, with different studies often reporting conflicting gene expression data (The Neuroscientist, Vol. 12, Number 4, 2006, pages 349-361; Abstract and page 351). Tsuang et al.

undertake an analysis that is very similar to the one in the instant specification. Regarding their results, Tsuang et al. caution that the results must be interpreted with caution given several limitations including small sample size, the fact that the findings are not replicated in a separate cohort and results "may represent chance findings and type-I inferential errors," and that the patients tested were all on drugs that were not accounted for in the analysis (American Journal of Medical Genetics, Part B (Neuropsychiatric Genetics) 133B:1-5(2005)). All of these cautions set forth by Tsuang et al. appear to be equally relevant to the study set forth in the instant application. Vawter et al. teach that there is lack of consistency in the study of genes differentially expressed in schizophrenia which might be related to etiological and genetic heterogeneity of the illness (p. 42, Vawter et al. Schizophrenia Research, Vol. 67, pages 41-52, 2004). Further, Vawter et al. teach that genes that are significant by a t-test may not exceed the threshold for fold of change to be considered above background expression (p. 46). All of these taken together underscore and highlight the very unpredictable nature of this technology area.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the post-filing art of Wu (2001). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The art of Newton

et al (2001) further teaches the difficulty in applying gene expression results. Newton et al. teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph). There is no replication of data in the instant specification.

Further, for claim 96, the data in the specification appear to support the opposite of what the practicing the method in the claims would suggest.

**Quantity of Experimentation**

The instant specification does not provide enabling support for the practice of a single embodiment within the claimed invention due to the lack of validation and replication of the observed differential expression of BTG2. In order to practice the claimed invention, one would have to replicate the experiments set forth in the specification on different populations of individuals in order to determine that any relative observation of a difference greater than 2 or 2.5 or even 2.46 is sufficient to conclude that schizophrenia is indicated. The issue here is that success is not guaranteed, and indeed the results remain highly unpredictable, as discussed by the references cited in the previous section. Thus, given the lack of teaching in the specification and the highly unpredictable nature of the technology, an extensive amount of work would be required to practice the claimed invention.

**Conclusion**

The claims include methods which encompass the detection in blood of the expression of BTG2 in a test subject and comparing this expression to control subjects, wherein the comparison itself "is indicative of schizophrenia," or some similar language. The identification of gene differential expression/disease indication relationships is a highly unpredictable

endeavor, requiring extensive experimentation. The specification provides minimal guidance. In light of the factors discussed, therefore, it is concluded that it would require undue experimentation to practice the claimed invention.

**Response to Remarks**

Applicant traverses the enablement rejection beginning on page 9 of the response. Applicant argues that the claims should be considered "formally enabled" if only to a "minimal extent." Here, the examiner has provided extensive discussion of the level of predictability in the technology area and the state of the prior art at the time of filing. These weigh heavily against the enablement of the claimed invention, especially in light of the small sample sizes used, and the failure to replicate the initial findings. Applicant argues that in the absence of contradictory information, the disclosed data is presumed to be informative to a given extent, regardless of the classification power conferred by the data beyond the minimum necessary to satisfy the plain language of the claims. However, again, applicant is pointed to the teachings in the literature which speak to the essential nature of replication and proper fitting in attempts to develop classification schemes, and the frequency with which initial findings are not able to be replicated, particularly in the highly complex field of schizophrenia diagnostics.

Applicant argues that the claimed methods have a specific and substantial utility. There is no rejection on the record under 101. The arguments are moot.

The rejection is modified to address the newly added claims, and maintained.

***Conclusion***

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday or Tuesday, from 9:00 AM until 4:30 PM, and Wednesday mornings from 8:00 AM until 12:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached by calling (571) 272-0763.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be

viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

October 8, 2009